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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,673	10/07/2003	Jeff L. Ellsworth	02-21	5506

7590 10/16/2007

ZymoGenetics, Inc.
1201 Eastlake Avenue East
Seattle, WA 98102

EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
10/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/680,673	ELLSWORTH, JEFF L.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-26* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 08/07/2007 has been entered. Claims 1–26 are pending. Claims 1–8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/06/2006. Claims 9–26 and the species high molecular weight hyaluronans are being examined.

Response to Arguments

Applicant's arguments with respect to claims 9–26 have been considered but are moot in view of the new ground(s) of rejection.

New Formal Matters, Objections and/or Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12–16 and 21–25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to or encompass "said administration further comprises ... methylcellulose," "said administration over time is accomplished using ... a putty," "said administration over time is accomplished using a reservoir system," or "said administration

further comprises an anti-inflammatory drug." The claim (claim 9 or 18) from which claims 12–16 and 21–25 depend directly or indirectly is directed to a method "comprising the step of administering … [an] admixture consisting of FGF18 and hyaluronic acid." Since the admixture administered consists of FGF18 and hyaluronic acid, the presently rejected claims are reasonably construed as encompassing an administration of the admixture consisting of FGF18 and hyaluronic acid that is separate from "said administration further comprises … methylcellulose," "said administration over time is accomplished using … a putty," "said administration over time is accomplished using a reservoir system," or "said administration further comprises an anti-inflammatory drug."

Although the present specification provides for the administration of FGF18 and hyaluronic acid separately or in combination as a single composition (paragraph bridging pages 10-11) the specification does not provide for an administration of an admixture consisting of FGF18 and hyaluronic acid that is separate from an administration that "comprises … methylcellulose," "is accomplished using … a putty," "is accomplished using a reservoir system," or "comprises an anti-inflammatory drug." This is a new matter rejection.

The examiner uses an ellipsis for brevity and not for limiting the rejection to "methylcellulose" and "putty".

The examiner relies on the following passages from the specification for concluding that the specification lacks support for the claimed invention:

> … the present invention is directed to compositions of FGF18 polypeptides or proteins plus negatively charged carriers, in particular hyaluronic acid for stimulating the proliferation of mesenchymal cells, particularly chondrocytes. Page 6, lines 5-12.

> FGF18 compositions can be applied by direct injection into the synovial fluid of the joint or directly into the defect, either alone or complexed with a suitable carrier for extended release of protein. Page 9, full paragraph 2.
>
> FGF18 can also be used to expand chondrocyte populations in culture for autogenous or allogenic chondrocyte transplantation and then administered with concurrent treatment consisting of administration of FGF18 polypeptide and HA compositions. Paragraph bridging pages 9-10.
>
> The FGF18 and HA may be administered separately or in combination as a single composition. Paragraph bridging pages 10-11.
>
> ...a pharmaceutical FGF18 and HA composition will comprise a formulation for timed-release of the protein. Time-release formulations generally include a monolithic delivery device comprising biocompatible solutions, gels, pastes, and putties in a matrix, in which the composition is entrapped or dissolved. Page 11, full paragraph 1.
>
> Although administration of FGF18 and HA, in a pharmaceutically acceptable admixture, is sufficient to provide the delivery of the chondrogenic peptides of the present method, there may be clinical situations where additional drugs are combined in the admixture. Page 11, full paragraph 2.

Applicant argues that the newly amended claims are supported by the claims as originally filed. Applicant's arguments have been fully considered but they are not persuasive. Claims 12–16 and 21–25 originally recited "said admixture further comprises ..." or "said admixture is ...". Neither phrase provides for an administration of an admixture consisting of FGF18 and hyaluronic acid that is separate from an administration that "comprises ... methylcellulose," "is accomplished using ... a putty," "is accomplished using a reservoir system," or "comprises an anti-inflammatory drug." Therefore, the newly amended claims are new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12–16 and 21–25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The present claims are directed to or encompass a "method ... comprising the step of administering ... a pharmaceutically admixture consisting of FGF18 and hyaluronic acid," "wherein said administration further comprises ... methylcellulose," "wherein said administration over time is accomplished using ... a putty," "wherein said administration over time is accomplished using a reservoir system," and "wherein said administration further comprises an anti-inflammatory drug." The examiner uses an ellipsis for brevity and not for limiting the rejection to "methylcellulose" and "putty".

The examiner is aware that the transitional phrase "comprising" in a method claim indicates that the claim is open-ended and allows for additional steps. Although the entire claimed method is presumptively open-ended, the "the step of administering" is not and consists of "the step of administering ... a pharmaceutically admixture consisting of FGF18 and hyaluronic acid." Thus, it is unclear how to construe these claims because it is unclear if "said administration" comprises administering an admixture that comprises FGF18, hyaluronic acid, and additional components such as methylcellulose, a putty, a reservoir system and an anti-inflammatory drug or if the additional components are administered separately from the admixture consisting of FGF18 and hyaluronic acid. The metes and bounds are not clearly set forth.

Claim Objections

Claims 12–16 and 21–25 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The present claims are directed to or encompass a "method … comprising the step of administering … a pharmaceutically admixture consisting of FGF18 and hyaluronic acid," "wherein said administration further comprises … methylcellulose," "wherein said administration over time is accomplished using … a putty," "wherein said administration over time is accomplished using a reservoir system," and "wherein said administration further comprises an anti-inflammatory drug." The examiner uses an ellipsis for brevity and not for limiting the objection to "methylcellulose" and "putty".

The examiner is aware that the transitional phrase "comprising" in a method claim indicates that the claim is open-ended and allows for additional steps. Although the entire claimed method is presumptively open-ended, the "the step of administering" is not and presumptively consists of "the step of administering … a pharmaceutically admixture consisting of FGF18 and hyaluronic acid." Thus, it is unclear how to construe these claims because it is unclear if "said administration" comprises administering an admixture that comprises FGF18, hyaluronic acid, and additional components such as methylcellulose, a putty, a reservoir system and an anti-inflammatory drug or if the additional components are administered separately from the admixture consisting of FGF18 and hyaluronic acid. The administration of an admixture comprising FGF18 and hyaluronic acid and additional components such as methylcellulose, a

putty, a reservoir system and an anti-inflammatory drug does not infringe the administration of an admixture consisting of FGF18 and hyaluronic acid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9–15, 17–24 and 26 rejected under 35 U.S.C. 103(a) as being unpatentable over Wobig (Clin Ther. 1999 Sep;21(9):1549-62) in view of Levin (U. S. Patent No. 6,677,321), Yayon (U. S. Patent No. 7,009,039), and Balazs (U. S. Patent No. 4,636,524).

In a study comparing the elastoviscous properties of a high-molecular-weight viscosupplement, hylan G-F 20, with those of a lower-molecular-weight hyaluronan in patients with osteoarthritis (OA) of the knee, it was found that the higher-molecular-weight, more elastoviscous hylan G-F 20 had significantly greater pain-relieving effects than did the lower-molecular-weight, less elastoviscous hyaluronan. The patients received three intra-articular injections at 1-week intervals, i.e., the "administration occurs over time." See Wobig, Abstract; page 1552, left column, full paragraph 1 and right column, full paragraph 1; paragraph bridging pages 1550-1551; page 1559, right column, last paragraph). In addition, hylan G-F 20 contains 20% hylan B, a highly hydrated gel, which gives it an infinite molecular weight (page 1551, left column, last full paragraph). In other words, the administration over time is accomplished using a solution or gel and the administration further comprises high molecular weight hyaluronans.

Wobig does not teach a method comprising the step of administering into a synovial cavity a pharmaceutically acceptable admixture consisting of FGF18 and hyaluronic acid.

Hylan G-F 20 is known in the art as Synvisc. See Levin, column 6, full paragraph 4. Levin also discloses the administration by intra-articular injection of compounds useful for treating an inflammatory joint disease (claim 25).

According to the present specification (paragraph bridging pages 3-4), the term "hyaluronic acid" includes both low and high molecular weight forms of hyaluronans and crosslinked hyaluronans or hylans, such as Synvisc.

Yayon discloses a freeze-dried, biocompatible, biodegradable matrix of plasma-derived proteins that is useful in methods for regenerating and/or repairing various tissues in vivo (paragraph bridging columns 7-8). The matrix can be utilized as an implantable scaffold in reconstructive surgery methods for regenerating and/or repairing tissue that have been damaged for example by trauma, surgical procedures or disease (column 8, full paragraph 1). Scaffold applications include the regeneration of cartilaginous tissues (column 8, full paragraph 2). Also included is the introduction into the sponge of an auxiliary component which is a bioactive agent selected from growth factors, cytokines, enzymes, anti-microbials, anti-inflammatory agents (column 9, full paragraph 1). In other embodiments the matrix includes hyaluronic acid (column 12, last full paragraph). Bioactive agents, such as FGF18, may be included in the matrix in order to enhance a therapeutic effect, such as cartilage healing. Incorporation of such agents into the matrix provides a slow-release or sustained-release mechanism. See column 13, full paragraph 1. In the reconstruction of structural tissues like cartilage and bone, tissue shape is integral to function, requiring the molding of the matrix into three dimensional configuration articles of

varying thickness and shape (column 11, full paragraph 3). The examiner construes Yayon's implantation as "surgical implantation." Damage to cartilage may result from a degenerative process such as such as osteoarthritis (column 1, lines 25-43). Therefore, the examiner concludes that mammals with osteoarthritis are in need of increased chondrocyte proliferation. Yayon does not teach a method comprising the step of administering into a synovial cavity a pharmaceutically acceptable admixture consisting of FGF18 and hyaluronic acid.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat patients with osteoarthritis (OA) of the knee by administering hylan G-F 20, as taught by Wobig, and to modify that teaching by administering FGF18, as taught by Yayon, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to obtain the analgesic effect of the hylan G-F 20 and the cartilage healing effect of FGF18. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art.

It is known in the art that cross-linked gels of hyaluronic acid can be used as drug delivery devices that slow down the release of a low molecular weight substance dispersed therein but not covalently attached to the gel macromolecular matrix. See, for example, Balazs, column 4, paragraph 5 through paragraph bridging columns 4-5. Balazs also notes that hyaluronic acid has the property of giving highly swollen cross-linked gels (column 2, full paragraph 2). It is apparent, therefore, that cross-linked gels of hyaluronic acid would allow the FGF18 to remain in place at the desired site and be delivered to the desired site over time to

effect an enhanced cartilage healing activity of the FGF18, rather than being washed away from the desired site by bodily fluids or diffusing away from the desired site. It is also apparent that cross-linked gels of hyaluronic acid are a "reservoir system."

Insofar as reconstructive surgery methods for regenerating and/or repairing cartilage are used for the treatment of damaged cartilage, then it would have obvious to one of ordinary skill in the at the time of applicant's invention to surgically implant an admixture consisting of FGF18 and hyaluronic acid at the time of surgery with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to obtain the analgesic effect of the hylan G-F 20 and the cartilage healing effect of FGF18.

It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention to allow growth of new cartilage tissue and surgically contour the new cartilage surface, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because in the reconstruction of structural tissues like cartilage, tissue shape is integral to function.

The invention is prima facie obvious over the prior art.

Claims 9, 16, 18 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wobig (Clin Ther. 1999 Sep;21(9):1549-62) in view of Levin (U. S. Patent No. 6,677,321), Yayon (U. S. Patent No. 7,009,039), and Balazs (U. S. Patent No. 4,636,524) as applied to claims 9 and 18 above, and further in view of Tice (U. S. Patent No. 4530840).

Wobig in view of Levin, Yayon, and Balazs teach a method of treating osteoarthritis in mammals comprising the step of administering into a synovial cavity a pharmaceutically

acceptable admixture consisting of FGF18 and hyaluronic acid, as discussed above. Wobig in view of Levin, Yayon, and Balazs do not teach administering into a synovial cavity an anti-inflammatory drug.

Inflammations of the various joints of the body are quite frequently manifestations of a disease such as osteoarthritis. In the treatment of the inflammation, an anti-inflammatory agent in injectable form is administered by intra-articular injection directly into the joint or joints which exhibit inflammation. See, for example, Tice, column 1, lines 14-44. Tice does not teach a method of treating osteoarthritis in mammals comprising the step of administering into a synovial cavity a pharmaceutically acceptable admixture consisting of FGF18 and hyaluronic acid.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat osteoarthritis in mammals by administering into a synovial cavity a pharmaceutically acceptable admixture consisting of FGF18 and hyaluronic acid, as taught by Wobig in view of Levin, Yayon, and Balazs, and to modify that teaching by further administering into a synovial cavity an anti-inflammatory drug, as taught by Tice, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to treat the inflammations of the various joints of the body that are quite frequently manifestations of a disease such as osteoarthritis. The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, MANJUNATH RAO, CAN BE REACHED AT (571)272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID ROMEO/
PRIMARY EXAMINER
ART UNIT 1647

DSR
OCTOBER 12, 2007